

Diagnosis-Related Criteria in the Consideration of Extracorporeal Membrane Oxygenation in Neonates Previously Treated With High-Frequency Jet Ventilation

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ABSTRACT. High-frequency jet ventilation (HFJV) is one of several high-frequency techniques that are particularly valuable for treating the neonate with lung disease refractory to conventional ventilation or with pulmonary air leak. Extracorporeal membrane oxygenation (ECMO) has also emerged as a valuable rescue therapy for neonates of more than 2000 g birth weight and 34 weeks' gestation with intractable respiratory failure. With the concurrent introduction of HFJV and ECMO, the authors sought to evaluate the role of HFJV prior to the institution of ECMO therapy. The data base for 2856 neonates receiving mechanical ventilation in one unit was used to identify 73 (of 298 total) neonates treated with HFJV, who were eligible by age and weight criteria for ECMO. Patients were grouped by diagnosis, and the oxygenation index (OI) was calculated during therapy. Outcome was evaluated for mortality, and the sensitivity of the OI for predicting mortality was calculated. Neonates who survived with HFJV alone presented with an OI of 0.30 ± 0.03 (SEM), significantly less than nonsurvivors (0.42 ± 0.04 , $P = .016$). Survivors responded to HFJV with a rapid decrease in OI at 1 hour (0.19 ± 0.02 , $P < .001$) and 6 hours (0.15 ± 0.01 , $P < .001$). Nonsurvivors did not respond significantly at 1 hour (OI = 0.33 ± 0.04 , $P =$ not significant [NS]) or at 6 hours (OI = 0.40 ± 0.06 , $P =$ NS). By diagnosis, neonates with respiratory distress syndrome survived more often with HFJV (28/34, 82%) than neonates with meconium aspiration (10/26, 38%) or diaphragmatic hernia (3/9, 33%). Neonates with respiratory distress syndrome seldom presented with high OI values, but the majority of those who did survived (5/7 survived with initial OI ≥ 0.40). Neonates with meconium aspiration and a single OI ≥ 0.40 on presentation fared much worse: 13 (87%) of 15 died. From these results, it appears that neonates with severe intractable respiratory distress syndrome and/or air leak are most likely to respond favorably within 6 hours of starting HFJV. In contrast, neonates with meconium aspiration respond far less well and may require early ECMO intervention, particularly with a single OI ≥ 0.40 . *Pediatrics* 1992;89:491-494; high-frequency jet ventilation, extracorporeal membrane oxygenation, neonate, respiratory distress syndrome, oxygenation index.

ABBREVIATIONS. HFV, high-frequency ventilation; ECMO, extracorporeal membrane oxygenation; HFJV, high-frequency jet ventilation; HiFi Trial, National Collaborative Study of High-frequency Oscillatory Ventilation; F_{iO_2} , fraction of inspired oxygen; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; MAS, meconium aspiration syndrome; CDH, congenital diaphragmatic hernia; OI, oxygenation index; NS, not significant.

High-frequency ventilation (HFV) and extracorporeal membrane oxygenation (ECMO) are two new techniques that have recently been used for the rescue treatment of neonates with severe and intractable respiratory disease. Several recent studies have suggested that HFV may be valuable for the neonate with lung disease that is refractory to conventional management or for the neonate with pulmonary air leak syndromes.¹⁻⁴ High-frequency jet ventilation (HFJV), in particular, appears to be an effective treatment for the child with pulmonary interstitial emphysema or tension pneumothorax.⁵ High-frequency jet ventilation allows continued ventilation at lower peak and mean airway pressures and results in more rapid resolution of air leaks, which often complicate neonatal ventilatory support. In contrast to these reported benefits of HFJV in the treatment of refractory disease and/or air leak, the National Collaborative Study of High-Frequency Oscillatory Ventilation (the HiFi Trial) failed to demonstrate any value in early application of high-frequency oscillatory ventilation in premature newborns.⁶ Subsequent commentary, however, has suggested that the approach used in the HiFi Trial may not have been optimal and that an alternative strategy of improved alveolar recruitment might have been more beneficial to neonates in the high-frequency oscillatory ventilation group.⁷ The HiFi Trial also failed to evaluate newborns of more than 2000 g birth weight, a group of patients who have received little attention in most reports of HFV experiences.

Extracorporeal membrane oxygenation has also emerged as a valuable rescue therapy for the critically ill neonate with intractable respiratory failure.^{8,9} Because of intracranial hemorrhage risk and technical limitations, ECMO has been used primarily in newborns of more than 2000 g birth weight and 34 weeks gestational age. Most studies evaluating the effectiveness of ECMO therapy have cited historical controls in which HFJV was not used. To date, HFJV and ECMO have been developed independently, and no

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investigations have examined the relative roles of HFJV and ECMO in the treatment of these neonates. With the introduction of HFJV and ECMO concurrently in many intensive care nurseries, it seems essential to establish the role of this form of treatment prior to institution of ECMO.

It is the purpose of this study, therefore, to review treatment with HFJV in our nursery for the neonate of more than 2000 g birth weight, at greater than 34 weeks' gestation and with severe neonatal lung disease; to identify among these neonates those who did not survive with HFJV alone; and to develop criteria from these data for the early initiation of ECMO in neonates who fail to respond to HFJV.

METHODS

The neonatal data base (Medical Data Systems, Wayne, PA) for the Division of Neonatology at the Children's Hospital of Philadelphia was reviewed for the period of time from January 1983 to May 1989. During that time, 2856 neonates were treated with mechanical ventilation. Of these newborns, 298 (10.5%) qualified for treatment with HFJV. Informed consent was obtained from parents prior to initiation of HFJV under a protocol approved by the Institutional Review Board of the Children's Hospital of Philadelphia and an Investigational Device Exemption from the Food and Drug Administration of the United States.

As previously reported,¹ entry criteria into the HFJV protocol included a prospective mortality assessment for neonates, which was considered to be between 85% and 90% prior to the initiation of HFJV. Additional factors considered for HFJV therapy included the following: Peak inspiratory pressure > 30 cm H₂O, usually with a fraction of inspired oxygen (F_{IO₂}) of 1.0; the presence of severe pulmonary interstitial emphysema or continued pneumothoraces; and failure to oxygenate above a P_{aO₂} of 40 mm Hg after a trial on conventional mechanical ventilation with an inspired oxygen of 100%. Further details of the technique of HFJV used (which was combined with background conventional mechanical ventilation) are reported in a previous paper from our group.¹ For the purposes of this study, persistent pulmonary hypertension of the newborn (PPHN) was diagnosed as a failure of hyperventilation to produce oxygenation at these ventilator settings.

Commonly applied ECMO criteria were used to select newborns from the HFJV population for inclusion in this retrospective data review. Newborns were included if they (1) were of more than 34 weeks' gestation; (2) were greater than 2000 g birth weight; and (3) had received conventional ventilator treatment for less than 7 days.

Neonates were thus identified from the HFJV data base who had received HFJV as rescue therapy after conventional ventilator management, similar to the standard approach for selection of ECMO candidates. These neonates were then grouped according to the following diagnostic categories: (1) respiratory distress syndrome (RDS), with prematurity and radiographic consistency; (2) meconium aspiration syndrome (MAS) and PPHN, in term newborns with meconium staining of the amniotic fluid and previously noted evidence of pulmonary hypertension; (3) sepsis and/or pneumonia, predominantly group B streptococcal infection, as documented by blood or tracheal aspirate culture; and (4) congenital diaphragmatic hernia (CDH).

The data base was further queried for descriptive information and outcome data for each infant. Initial conventional and HFJV ventilator settings were noted, as well as arterial blood gas values and F_{IO₂} at 1 hour prior to HFJV, 1 hour following initiation of HFJV, and 6 hours after initiation of HFJV. The oxygenation index (OI) values at these time intervals were calculated according to the standard definition:

$$OI = \overline{Paw} \times F_{IO_2} / P_{aO_2}$$

Mean airway pressure (\overline{Paw}) values were calculated in neonates from the airway pressure measured by the High Frequency Jet Ventilator (Life Pulse, Bunnell, Inc, Salt Lake City, UT) at the distal trachea and displayed on the face panel of the ventilator. The mean airway pressure on the conventional ventilator, prior to initiation of HFJV, was measured at the same site, through a triple lumen

endotracheal tube (Hi-Lo Tube, Mallinckrodt, Inc, St Louis, MO). Thus, mean airway pressures prior to and following initiation of HFJV were derived in a similar manner.

Differences in mean OI were calculated between the initial OI 1 hour prior to HFJV therapy and the OI at 1 and 6 hours after initiation of HFJV treatment. These values were compared using analysis of variance and the dependent Student's *t* test. Incidences of survival were calculated for each of the previously mentioned diagnostic categories. The OI was also used to calculate sensitivity and specificity in detecting death as an outcome in each diagnostic category and for the study population overall.

RESULTS

Seventy-three (24%) of the 298 newborns treated with HFJV during this time period met ECMO criteria in retrospect and qualified for inclusion in this review. Of these 73 subjects, 45 (62%) survived and 28 (38%) died. There were no differences between median weights and gestational ages for survivors and non-survivors. Median weights were 3300 g and 3200 g, respectively. The gestational ages for survivors ranged from 34 to 42 weeks, while nonsurvivors' ages ranged from 34 to 43 weeks. Hypoxemia, failure of conventional mechanical ventilation, and recurring air leaks were equally prevalent as criteria for entry into the HFJV protocol in both groups. Survivors received mechanical ventilation (both HFJV and conventional) for a range of 1 to 23 days before extubation. Non-survivors received HFJV and conventional ventilation for a range of 1 to 22 days. High-frequency jet ventilation was started at a mean of 3.5 ± 0.6 (SEM) days in survivors, compared with 2.4 ± 0.5 days in non-survivors ($P =$ not significant [NS]). The duration of HFJV treatment, however, did differ, with the survivors receiving treatment for a mean of 2.7 ± 2.9 days, while non-survivors were treated for only 1.5 ± 1.4 days ($P < .001$).

Figure 1 displays the OI values for survivors and non-survivors prior to HFJV and at 1 and 6 hours following initiation of HFJV treatment. Survivors presented prior to HFJV with a mean OI significantly lower than non-survivors. Mean OI for survivors was 0.30 ± 0.03 (SEM) compared with an OI of 0.42 ± 0.04 ($P = .016$) in non-survivors. In neonates who survived, the OI decreased within 1 hour to a mean of 0.19 ± 0.02 ($P < .001$, compared with pre-HFJV OI) and by 6 hours was 0.15 ± 0.01 ($P < .001$, compared with pre-HFJV OI). In contrast, the OI for non-survivors did not decrease significantly (OI = 0.33 ± 0.04 , $P = .13$) and by 6 hours, showed no difference

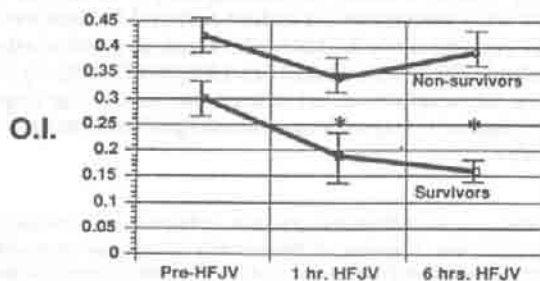


Fig 1. Change in oxygenation index (O.I.) pre-high-frequency jet ventilation (pre-HFJV), 1 hour following initiation of HFJV, and 6 hours after starting HFJV treatment (mean \pm SEM). Analysis of the response to HFJV by comparative regression analysis of variance demonstrated significant improvement in survivors with HFJV vs non-survivors (* $P < .001$).

(OI = 0.40 ± 0.06 , $P = .8$) compared with pre-HFJV values. Analysis of variance regression analysis of the response of survivors compared with that of nonsurvivors revealed a significantly better response to HFJV in survivors ($P < .001$).

Figure 2 demonstrates the survival rates for each of the diagnostic categories reviewed. In the group of neonates with RDS, 28 survived, while only 6 died, for a survival rate of 82%. For the neonates with MAS/PPHN, 10 survived and 16 died (38% survival). Three (33%) of 9 neonates with a CDH survived. All 4 newborns (100%) with sepsis and pneumonia survived.

In the group of neonates who survived, 7 (16%) had an OI ≥ 0.40 prior to HFJV treatment. Five of these neonates had RDS, while 2 had MAS. In all of these cases, the OI decreased rapidly on initiation of HFJV, decreasing to a mean of 0.16 ± 0.6 by 6 hours ($P < .01$). In contrast, 19 nonsurvivors had an OI greater than 0.40 prior to HFJV. Thirteen (68%) of these neonates had MAS/PPHN, 4 (21%) had a CDH, and 2 (11%) had RDS. In only 6 cases (4 MAS/PPHN, 1 RDS, 1 CDH) did the OI decrease below 0.40 by 6 hours of treatment. The mean OI at 6 hours of treatment was 0.52 ± 0.08 ($P = NS$, compared with pre-HFJV) for all nonsurvivors who had a pre-HFJV OI ≥ 0.40 . For all newborns ($n = 26$) with an OI ≥ 0.40 prior to HFJV, the survival rate was 27%. Only 2 (13%) of 15 newborns with MAS/PPHN who had an OI ≥ 0.40 survived with HFJV. Although the sample size was small for the CDH and pneumonia subgroups, the mortality data and OI data for nonsurvivors (Fig 1) accurately describe those newborns who failed to respond to HFJV intervention.

Sensitivity and specificity of the OI at a value ≥ 0.40 for detecting subsequent mortality and survival were also examined prior to HFJV, and at 1 and 6 hours following initiation of treatment, as seen in the Table. Newborns who had a single OI ≥ 0.40 at any time in this study had a subsequent overall mortality rate of 69%. The sensitivity of the OI decreased after initiation of HFJV. Decreasing the OI to a value lower than 0.40 did not improve sensitivity for early detection of subsequent mortality in these newborns. Diagnostic subgroups did not alter these observations when adequate numbers of newborns (≥ 10) were examined.

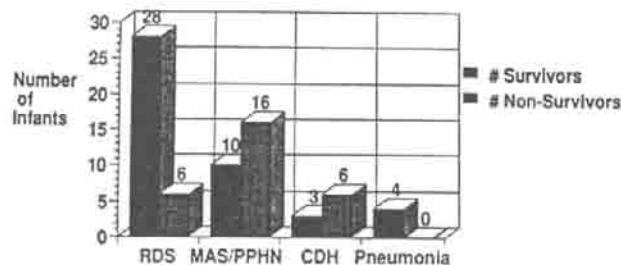


Fig 2. Survival rates for infants in the various diagnostic categories. Figures above histogram bars indicate absolute numbers of survivors and nonsurvivors. RDS, respiratory distress syndrome; MAS/PPHN, meconium aspiration syndrome and persistent pulmonary hypertension of the newborn; CDH, congenital diaphragmatic hernia; pneumonia, group B streptococcal pneumonia and sepsis.

DISCUSSION

This study demonstrates that ECMO-eligible infants with RDS refractory to conventional ventilation or complicated by air leaks may respond to HFJV when used as a rescue therapy. In contrast, babies with MAS or persistent pulmonary hypertension appear to respond far less satisfactorily, particularly when the OI is above 0.40. In all categories of newborns examined, a rapid decrease in the OI by 6 hours of age appeared to be a critical component for successful HFJV treatment. A single OI value above 0.40 was associated with a mortality rate of approximately 70% and appeared to be a criterion for early use of ECMO as a possible life-saving modality. Furthermore, initial intervention with HFJV may obscure the sensitivity of the OI as an early indicator for timely institution of arteriovenous bypass.

With the introduction of both HFJV and ECMO as approaches for the rescue treatment of neonates with severe respiratory illness, the question of which therapy is "better" has been posed. Furthermore, historical criteria for initiation of ECMO have not included concurrent use of HFJV to date. As a result, the neonatologist is often uncertain about which of these two very different strategies represents the optimal management approach. High-frequency jet ventilation offers the advantage of potentially lowering airway pressures and minimizing barotrauma, without necessitating the sacrifice (or temporary interruption) of the carotid artery and jugular vein for cannulation and bypass therapy with ECMO.¹ Extracorporeal membrane oxygenation, because of its attendant risks of hemorrhage, infarction, neurologic injury, and sepsis, has usually been reserved as a "final resort," when all else has failed. Previously, the only work that attempted to examine the combined role of HFV and ECMO looked at oscillatory HFV and demonstrated that 21 (100%) of 21 oscillated neonates survived, with a tendency toward a more premature population and clinical evidence of pneumonia in more than half the cases.¹⁰ Gestationally more mature newborns with oxygenation failure received ECMO, with a survival rate of 88%. The authors recommended a staged support to rescue, with an attempt at oscillation first and ECMO only if that failed.

In contrast to that paper, the current paper looks at the difference in response to HFJV by diagnosis and severity of illness. Neonates who qualify for ECMO because of their size, gestational age, and postconceptional age vary in their response to HFJV. Neonates with RDS (eligible by those considerations for ECMO) appear to respond best to HFJV, showing a rapid decrease in their OI and a survival rate of 82%. Neonates with MAS/PPHN and CDH do not respond

TABLE. Sensitivity and Specificity of the Oxygenation Index (OI) for Predicting Mortality and Survival*

	Pre-HFJV	1 Hour Post-HFJV	6 Hours Post-HFJV
Sensitivity	50	32	32
Specificity	82	91	100

* Sensitivity = OI ≥ 0.40 in nonsurvivors/total nonsurvivors, and specificity = OI < 0.40 in survivors/total survivors. Values are percentages. HFJV, high-frequency jet ventilation.

as well, with a survival rate of approximately 35%. Neonates who did not respond to HFJV generally had a rapid downhill course, as seen by the fact that nonsurvivors in this study received HFJV for a significantly shorter time than did survivors.

For most newborns, however, it appears that a staged approach can be used. In the child with severe neonatal lung disease that is complicated by pulmonary air leak, or respiratory failure that requires higher than usual levels of support, HFJV should be initiated. The OI should be calculated before HFJV is started. In newborns with a high probability of survival, one should see a rapid decline in the OI, with a level below 0.20 achieved by 6 hours of treatment. Failure to observe such improvement, especially if there has been an OI greater than 0.40, should alert the clinician that the child has a high probability of dying. Extracorporeal membrane oxygenation should be considered at that time. In patients with MAS/PPHN who present with severe respiratory failure and an OI \geq 0.40, ECMO may be the treatment of first choice. One must be aware also that, once HFJV is started, the OI becomes increasingly less sensitive as a tool for predicting mortality.

The experience with HFJV that is reported in this paper was examined to identify neonates who were unlikely to survive without timely ECMO intervention. From these results, it appears that RDS and pneumonia are most likely to be benefited by HFJV treatment. In contrast, MAS/PPHN and CDH appear to respond far less well and may require early ECMO intervention. Assessment of these rescue interventions for neonatal respiratory failure should be carried

out in each nursery in order to minimize needless and unnecessarily risky interventions.

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